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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/075,616	02/15/2002	Martin P. Redmon	4821-464	2810

20582 7590 03/16/2004

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EXAMINER	
CHANNAVAJJALA, LAKSHMI SARADA	
ART UNIT	**PAPER NUMBER**
1615	

DATE MAILED: 03/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/075,616	REDMON ET AL.	
	Examiner	Art Unit	
	Lakshmi S Channavajjala	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 12--42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 12-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt of request for extension of time, amendment and remarks all dated 11-26-03 is acknowledged.

Claims 1-3, 5-10, 12-42 are pending. Claims 4 and 11 have been canceled.

Response to Arguments

Applicant's arguments filed 11-26-03 have been fully considered but they are not persuasive.

1. Claims 1-3, 5, 6, 25-28 and 41are rejected under 35 U.S.C. 103(a) as being unpatentable over Woosley et al or Woosley in view of in view of Blaug et al and Castello et al.

WO teaches a pharmaceutical composition comprising norastemizole, a derivative of astemizole, for the treatment of allergic disorders such as allergic rhinitis (page 4, lines 1-8), with and without lactose. Example 4 of WO does not contain lactose and accordingly reads on lactose-free formulation. The treatment comprises administration of norastemizole in an amount of 1-200 mg, as claimed in the instant invention, in a pharmaceutically acceptable carrier or excipient (page 6, lines 7-13). WO also teaches various routes and dosage forms for the administration of norastemizole (page 9, lines 33-39). In addition, WO teaches excipients such as binders, diluents, disintegrants, lubricant etc., are also disclosed in the solid pharmaceutical norastemizole composition (page 10, lines 24-32 and examples 4 and 5 on page 16). The formulations exemplified by WO also teach lower concentrations of STARCH 1500 and magnesium stearate. WO teaches norastemizole formulations with and without the presence of lactose. WO does not specifically recognize the incompatibility of norastemizole and lactose-

based excipients. Further, WO teaches both capsules and tablet forms containing norastemizole, and granules, powders, as well as coated formulations (page 10, lines 24-37). However, while the capsule of WO lack lactose, the tablets of WO are not free of lactose.

Blaug et al and Castello et al teaches that formulations containing amine salts, and teach that lactose and other sugars rapidly degrade the amines due to the amine base-carbonyl interaction, in the presence of high heat and moisture. The amine base is released due to a reaction of the alkaline lubricant such as magnesium stearate, which in turn form stearic acid, furnishing alkaline medium in the adsorbed moisture. Although Blaug et al and Castello et al do not specifically teach norastemizole formulations containing lactose, as acknowledged by applicants in the instant specification, norastemizole is an amine containing compound (chemical name is N-(4-piperidynyl)-1H-benzimidazole-2-amine that is sensitive to amine base-carbonyl interaction. Therefore, a skilled artisan possessing the teachings of Blaug et al and Castello et al would expect degradation of norastemizole in the presence of lactose, lubricants such as magnesium stearate, and factors such as high humidity and temperature. Therefore, it would have been obvious for a skilled artisan at the time of the instant invention to eliminate lactose and other sugars from the formulations containing amines as active ingredients or to carefully optimize the amounts of various excipients such as magnesium stearate, lactose and other sugars, and also control the moisture, temperature of the formulation so as to avoid degradation of norastemizole. Further, it would have been obvious for one of an ordinary skill in the art to eliminate lactose, irrespective of the dosage form i.e., tablet or capsule with an expectation to avoid the undesired interaction of lactose with the drug norastemizole.

3. Claims 9, 10, 12, 13, 22-24, 29-32 and 37-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woosley et al (WO 94/07495) (hereafter WO) or Woosley in view of Blaug et al and Castello et al and further in view of Remington: The science and practice of Pharmacy (Remington's).

The teachings of WO discussed above, contain disintegrants but not the claimed croscarmellose sodium and microcrystalline cellulose.

Remington's teaches oral dosage forms such as tablets, capsules etc., dosage forms and the addition of various additives or excipients that help in the preparation of the dosage forms, such as lubricants, diluents, binders and glidants or those that impart additional physical characteristics to the tablets such as disintegrants, colors, flavors, etc. Among the first group, Remington's teaches kaolin, calcium sulfate, dry starch, microcrystalline cellulose etc (as diluents, page 1617); gelatin, sugars, gum, cellulose derivatives, PVP etc (as binders, page 1617); lubricants talc, oils, magnesium stearate, aluminum stearate, PEG, etc., (as lubricants, page 1618) and croscarmellose sodium, sodium starch glycollate etc., (as disintegrants (page 1619). Particularly, Remington's teaches croscarmellose sodium as a super disintegrant, which is effective as it swells 4 to 8 fold in less than 10 seconds, followed by sodium starch glycolate that swells 7 to 12 fold in <30 seconds. It would have been obvious for one of an ordinary skill in the art at the time of the instant invention to use the appropriate excipients in the lactose-free composition of Woosley, with an expectation to achieve the desired properties for preparing dosage forms or physical properties. Further, optimizing the amounts of the additives for their art recognized effect would have been within the scope of a skilled artisan.

4. Claims 7, 8, 14-21, 33-36 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woosley et al (WO 94/07495) (hereafter WO) or Woosley ion view of Blaug et al and Castello et al, and further in view of Gilis et al.

WO does not teach coated particles of norastemizole. However, WO teaches coated dosage forms and granules or powders containing norastemizole (page 10). WO teaches norastemizole powders or granules (page 11), which read on particles. Examiner notes instant claims do not state any particular size of the particles. WO does not teach coated norastemizole.

Gilis et al teaches extended release of astemizole in film-coated tablets for the treatment of allergic disorders such as allergic rhinitis (column 1, lines 11-34), in particular micronized astemizole (col.3, lines 10-13). Gilis also teaches a combination of an antihistamine and a decongestant such as pseudoephedrine in the composition. In order to avoid contact of the medicament with water vapor, Gilis et al teaches the packaging of coated tablets into blister packs (column 4, lines 40-43). Gilis teaches astemizole preparation coated with film forming polymers for extended release and teaches the claimed polymers in col. 2-col. 3. In particular, see col. 3, lines 10-37.

Gilis does not teach norastemizole and only teaches astemizole. However, WO recognizes both astemizole and norastemizole are equally effective in their therapeutic activity and norastemizole lacks the adverse effects of astemizole. Therefore, it would have been obvious for a skilled artisan to choose lactose-free, norastemizole-containing composition of WO and coat with film-forming polymers of Gilis because the polymers of Gilis provide extended release of norastemizole and thus avoids repeated administration of the drug.

RESPONSE:

Rejection over WO (Woosley alone) or WO in view of Blaug et al and Castello et al:

WO (Woosley): Applicants argue that WO merely teaches norastemizole for the treatment of allergic disorders but does not recognize tablet forms without lactose except lactose-free capsules, (example 4 of WO). Applicants argue that lactose; a common excipient of tablets is incompatible with norastemizole, which is not recognized by WO. Therefore, applicants argue that WO does not provide a reasonable expectation of success in formulating a lactose-free tablet. However, the formulation (capsule) of WO is suggestive of a formulation containing norastemizole without lactose. Further, in response to applicants' argument that the presence of lactose, a common excipient of tablets, is incompatible norastemizole, which is nor recognized by WO, examiner notes that instant specification only shows capsule formulation without lactose but does not show the effect of lactose on the preparation of tablet containing norastemizole. Furthermore, the specification states that the composition can be in either form. Therefore, in the absence of criticality it would have been obvious for a skilled artisan at the time of the instant invention to prepare dosage forms without lactose and prepare them as a capsule or a tablet and still expect the same therapeutic effect of norastemizole.

Blaug and Castello: Applicants argue that while Castello et al and Blaug et al found incompatibility of primary amines with lactose, instant norastemizole is a secondary amine and not a primary amine. Further, applicants cite the reference of Hartaure et al (from specification) showing that secondary amines such as theophylline do not show any reaction with lactose. Thus, applicants argue that while it is known in the art that secondary amines do not react with

lactose, it was inventors who found an incompatibility of lactose with norastemizole. Therefore, applicants argue based on a primary amine interaction with lactose one of an ordinary skill in the art cannot expect the same reaction of a secondary amine with lactose. However, it is evident from applicants' reference to Hartaure et al that not all secondary amines behave the same way with lactose. Further, applicants have not shown any adverse effect of lactose on norastemizole in a *tablet* form. Therefore, one of an ordinary skill in the art would recognize that that lactose reacts with amine containing drugs resulting in discoloration or formation of a Schiff's base, and because norastemizole is an amine containing drug, one of an ordinary skill in the art would have prepared a lactose-free dosage form of norastemizole, in the form of a capsule or a tablet, with an expectation to avoid the adverse effects of lactose upon interaction with norastemizole. Accordingly, the rejection has been maintained.

Rejection over WO (Woosley alone) or WO in view of Blaug et al and Castello et al and further in view of Remington (The Science and Practice of Pharmacy):

Applicants' argue that Remington does not remedy the deficiencies of WO or Blaug or Castello i.e., lack of lactose-free formulation of norastemizole in the form of a tablet. However, applicants' arguments regarding WO, Blaug and Castello have been considered and examiner's position has been explained in the preceding paragraph. Remington has not been cited for lactose-free formulation and instead for microcrystalline cellulose, which applicants did not argue. Accordingly, for the reasons mentioned in the outstanding office action, it is examiner's position that the above rejection is proper.

Rejection over WO (Woosley alone) or WO in view of Blaug et al and Castello et al and further in view of Gilis:

Applicants argue that Gilis does not remedy the deficiencies of Woosley, Blaug or Castello because a mere disclosure that an antihistamine and pseudoephedrine can be combined in a compostion does not remedy deficiency of lack of lactose-free disclosure in Woosley and others. Applicants argue that instant claims require compositions comprising individually coated particles of norastemizole, whereas Gilis teaches a coating for a tablet containing astemizole suspended in a low viscosity polymer. Applicants argue that coating the norastemizole particles individually allows for mixing the particles with other excipients, and avoids the incompatibility. Applicants argue that the cited references fail to teach individual coating before being admixed with other excipients. Applicants' arguments are not found persuasive because instant comprising language allows for the presence of other excipients. Further, applicants have not shown any comparative advantage of coating the individual particles as opposed to coating the composition of norastemizole comprising other excipients. Furthermore, Blaug and Castello teach the effect of lactose on amine contaiuning drugs. Therefore, in the absence of any unexpected advantage of coating particles of norastemizole, one of an ordinary skill in the art would have readily recognized a suitable coating on the norastemizole particles and still achieve the desired release pattern of the drug.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S. Channavajjala whose telephone number is 703-308-2438. The examiner can normally be reached on 7.30 AM -4.00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on 703-308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-7921 for regular communications and 703-308-7921 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Lakshmi Channavajjala
Patent Examiner
Art Unit 1615
March 8, 2004

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
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